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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,779	10/29/2003	Fusao Tomita	506.40345VX1	6721

20457 7590 05/16/2006

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,779	TOMITA ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-23,25-27,29 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-23,25-27,29 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/901,884.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 19-23, 25-27, 29, and 33-38 are pending in the application.

[2] Applicant's amendment to the specification, filed on 3/6/2006, is acknowledged.

Election/Restriction

[3] Applicant's election with traverse of Group I, claims 19-23, 25-27, 29, and 33-38 reciting SEQ ID NO:9 in the reply filed on 3/6/2006 is acknowledged. The traversal is on the ground(s) that the DNA of claim 19 requires a selection of one DNA from *each* of the eight recited groups. Thus, applicant clarifies claim 19 as meaning that the DNA comprises at least eight distinct DNAs, wherein each of the eight DNAs is selected from each of the eight groups recited therein. In view of applicant's clarification of the meaning of the claim, the restriction between Groups I-VIII is withdrawn.

Priority

[4] Applicant's claim to domestic priority under 35 USC § 121 to US non-provisional application 09/901,884, filed on 7/9/2001, is acknowledged. The domestic priority claim is perfected in view of the specification amendment filed on 3/6/2006.

[5] Applicant's claim to foreign priority under 35 USC § 119(a)-(d) to JP 2000-234317, filed on 8/2/2000, in the declaration filed on 10/29/2003 is acknowledged. A certified copy of the foreign priority document has been filed in the 09/901,884 application.

Information Disclosure Statement

[6] All references cited in the information disclosure statement, filed on 10/29/2003, have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Specification/Informalities

[7] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 16, line 4) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Objections

[8] In order to maintain consistency in the claims, it is suggested that applicant insert a colon after "1(b)" in claim 19.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[9] Claim(s) 19-23, 25-27, 29, and 33-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 19 (claims 22-23, 25-27, and 29 dependent therefrom) is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent." What hybridization conditions are considered "stringent" varies widely in the art depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of SEQ ID NO:9-16 a nucleic acid must be to be included within the scope of the claim. It is suggested that applicant clarify the meaning of the term "stringent conditions."

[b] Claim 19 (claims 22-23, 25-27, and 29 dependent therefrom), claim 20 (claims 33, 35, and 37 dependent therefrom), and claim 21 (claims 34, 36, and 38 dependent therefrom) are indefinite in the recitation of "represented by" as it is unclear how homologous to the nucleic acids of SEQ ID NO:9-16 or to the polypeptides of SEQ ID NO:1-8 a sequence must be to included within the scope of the claims. Is the term meant to be interpreted as meaning the nucleic acids of SEQ ID NO:9-16 or the polypeptides of SEQ ID NO:1-8, or is it meant to be interpreted as some undefined "representation" thereof. It is suggested that applicant clarify the meaning of the term "represented by" by, for example, replacing the term "represented by" with "of."

[c] Claim 19 (claims 22-23, 25-27, and 29 dependent therefrom) is unclear in the recitation of "a protein exerting F0F1-ATPase activity when the protein forms a

complex..." In view of the disclosure of the specification, it would appear that it is the protein *complex* and not the individual protein subunit that is "exerting" (interpreted as having) F0F1-ATPase activity. It is suggested that applicant clarify the meaning of the phrase "a protein exerting F0F1-ATPase activity when the protein forms a complex..." in the claim.

[d] Claims 22-23 are indefinite in the recitation of "derived from" as it is unclear as to the meaning of the term. Is the term meant to indicate a source of the DNA, indicate that the DNA is a DNA "derivative," or a combination of these meanings? It is suggested that applicant clarify the meaning of the term.

[e] Claims 29 and 37-38 recite the limitation "the F0F1-ATPase activity." There is insufficient antecedent basis for this limitation in the claims. It is suggested that, for example, applicant delete "the" in both occurrences of "the F0F1-ATPase activity" in the claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[10] Claims 19-23, 25-27, 29, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 19 (claims 22-23, 25-27, and 29 dependent therefrom) is drawn to a genus of DNAs comprising a DNA "represented by" SEQ ID NO:9-16 or variants thereof that hybridize under "stringent conditions" and encode a protein that has F_0F_1-ATPase activity when combined with the others. Claim 20 (claims 33, 35, and 37 dependent therefrom) is drawn to a DNA comprising a genus of nucleotide sequences that are "represented by" SEQ ID NO:9-16. Claim 21 (claims 34, 36, and 38 dependent therefrom) is drawn to a DNA comprising a nucleotide sequence that is "represented by" SEQ ID NO:21.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the

specification discloses only a single representative species of the claimed genus of DNAs, i.e., SEQ ID NO:21. Other than this single species, the specification fails to disclose other representative species of the genus of claimed or recited DNAs. In this case, the genus of DNAs encompasses widely variant species, including any DNA "represented by" SEQ ID NO:9-16 or variants thereof that hybridize under "stringent conditions" and encode a protein that has F_0F_1-ATPase activity when combined with the others. The disclosure of the single representative species of SEQ ID NO:21 fails to reflect the variation among the members of the genus.

Given the lack of description of a representative number of compounds, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[11] Claim(s) 19-23, 25-27, 29, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:1-8, does not reasonably provide enablement for all DNAs encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are

summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 19 (claims 22-23, 25-27, and 29 dependent therefrom) is so broad as to encompass all DNAs "represented by" SEQ ID NO:9-16 or variants thereof that hybridize under any "stringent conditions" and encode a protein that has F_0F_1-ATPase activity when combined with the others. Claim 20 (claims 33, 35, and 37 dependent therefrom) is so broad as to encompass all DNAs comprising a nucleotide sequences that is "represented by" SEQ ID NO:9-16. Claim 21 (claims 34, 36, and 38 dependent therefrom) is so broad as to encompass all DNAs comprising a nucleotide sequence that is "represented by" SEQ ID NO:21. The broad scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the number of DNAs broadly encompassed by the claims. In this case the disclosure is limited to nucleic acids encoding SEQ ID NO:1-8.

The state of the prior art; The level of one of ordinary skill; The level of predictability in the art: The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of

which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The state of the art provides evidence for the high level of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. The reference of Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions." The teachings of Branden et al. are evidenced by Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that just a single amino acid substitution results in conversion of the parent

polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647).

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed polynucleotide, i.e., SEQ ID NO:21. Other than this single working example, the specification and prior art fail to provide the necessary specific guidance for making the entire scope of polynucleotides as noted above, including guidance regarding those nucleotides of SEQ ID NO:21 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity/utility.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or making variants of a given nucleic acid were known in the art at the time of the invention, e.g., hybridization or mutagenesis, it was not routine in the art to screen for all DNAs having a substantial number of substitutions or modifications as encompassed by the instant claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of non-routine experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable

correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[12] Claim(s) 19-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Sekine et al. (Abstracts of the Annual Meeting of the Society for Bioscience and Bioengineering, page 80, Japan, July 10, 2000; cited in IDS filed on 10/29/03). The claims are drawn to a DNA comprising DNA "represented by" SEQ ID NO:9-16 or variants thereof that hybridize under "stringent conditions" and encode a protein that has F_0F_1-ATPase activity when combined with the others, optionally wherein the DNA is "derived from" *Corynebacterium* or *Corynebacterium ammoniagenes,* a DNA comprising

nucleotide sequences that are "represented by" SEQ ID NO:9-16, and a DNA comprising a nucleotide sequence that is "represented by" SEQ ID NO:21.

Sekine et al. teaches the cloning of a *Corynebacterium ammoniagenes* F0F1-ATPase gene, encoding eight different subunits, and discloses a method for isolation thereof. This anticipates claims 19-23 as written.

While it is noted that Sekine et al. do not disclose the sequence of their nucleic acid, because the gene is a *C. ammoniagenes* F0F1-ATPase gene, it inherently has the same structure as that of SEQ ID NO:21.

[13] Claim(s) 19-21, 25-27, and 33-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Santana et al. (*J Bacteriol* 176:6802-6811, 1994; cited in the IDS filed on 10/29/03). Claims 19-21 are drawn to DNAs as noted above. Claims 25-27 and 33-36 are drawn to recombinant DNAs comprising said DNAs of claims 19-21 and transformants comprising said recombinant DNAs.

Santana et al. teaches the cloning of a *Bacillus subtilis* F0F1-ATPase gene, encoding eight different subunits, inserting the gene into a vector, and transforming *E. coli* with the vector (p. 6803, right column). This anticipates claims 19-21, 25-27, and 33-36 as written.

While it is noted that the nucleotide sequences of SEQ ID NO:21 and the *Bacillus subtilis* F0F1-ATPase gene of Santana et al. do not appear to be identical, the *Bacillus subtilis* F0F1-ATPase gene of Santana et al. would meet the limitations of claims 19-21 in view of the indefinite recitation of "represented by."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[14] Claim(s) 25-27, 29, and 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sekine et al. Claims 25-27 and 33-36 are drawn to recombinant DNAs and transformants as noted above. Claims 29 and 37-38 are drawn to methods for producing a protein by culturing a transformant.

The reference of Sekine et al. discloses the teachings described above. Sekine et al. further teaches a desire to create "metabolic mutants of *C. ammoniagenes* using genetic engineering." Sekine et al. does not teach inserting the gene into a vector, transforming a host cell with said vector, and producing a polypeptide using the resulting transformant.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to insert the gene of Sekine et al. into an expression vector, transform a host cell with said vector, and produce a polypeptide using the resulting transformant. One would have been motivated to this in order to initially characterize the protein in order to create "metabolic mutants of *C. ammoniagenes* using genetic engineering" as taught by Sekine et al. One would have a reasonable expectation of success for inserting the

gene of Sekine et al. into an expression vector, transforming a host cell with said vector, and producing a polypeptide using the resulting transformant in view of the state of the art at the time of the invention, which was well-developed in the art of recombinant protein expression. Therefore, claims 25-27, 29, and 33-38, drawn to recombinant DNAs, transformants and methods as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

[15] Claim(s) 29 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santana et al. Claims 29 and 37-38 are drawn to methods as described above.

The reference of Santana et al. discloses the teachings described above. Santana et al. further teaches that, while *B. subtilis* is "the most extensively studied gram-positive bacterium," "very little is known about oxidative phosphorylation" in the microorganism (p. 6803, left column). Santana et al. does not teach a method for producing a polypeptide using a transformant comprising the gene incorporated into a vector.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to insert the gene of Santana et al. into an expression vector, transform a host cell with said vector, and produce a polypeptide using the resulting transformant. One would have been motivated to this in order to characterize the protein in order to enhance understanding of oxidative phosphorylation in *B. subtilis* as suggested by Santana et al. One would have had a reasonable expectation of success for inserting

the gene of Santana et al. into an expression vector, transforming a host cell with said vector, and producing a polypeptide using the resulting transformant in view of the state of the art at the time of the invention, which was well-developed in the art of recombinant protein expression. Therefore, claims 29 and 37-38, drawn to methods as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[16] Status of the claims:

- Claims 19-23, 25-27, 29, and 33-38 are pending.
- Claims 19-23, 25-27, 29, and 33-38 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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